

REMARKS

Upon entry of this amendment, claims 1, 2, 6-11, 20, and 21 will be in the application. In the Advisory Action of June 6, 2003, the Examiner maintained the rejection under 35 USC 102(e) over Heideran *et al.* (U.S. 6,609,670). Heideran *et al.* do not anticipate the present claims. The present claims call for the use of collagen (either type I or type II) with BMP-4 or with a combination of BMP-4 and GDF-5, to induce or enhance chondrogenesis. Heideran *et al.* do not disclose use of collagen because there is modification by cross-linking to a polysaccharide, thereby modifying the collagen so that it is no longer collagen. Furthermore, nowhere in Heideran *et al.* is it stated that BMP-4 or GDF-5 induce or enhance chondrogenesis. The Examiner cites column 2, lines 7-10 of Heideran *et al.*, but that is directed to a collagen-polysaccharide matrix, not collagen. The Examiner also cites column 2, lines 53-61 pointing a definition of "tissue repair". However, Heideran *et al.* are directed to the treatment of a bone tumor, defined at column 2, lines 47-52. Treatment of bone tumor is directed to the minimizing or the eliminating of tumor cells. Moreover, in the reference cited by the Examiner, Hattersley *et al.* (U.S. 5,902,785) it is stated in column 2, that BMP-4 (line 44) is a protein useful for induction of osteocytes and bone tissue, whereas BMP-12, BMP-13, or BMP-52 (lines 42-43) are useful for the induction of chondrocytes and cartilage and soft tissue. Therefore, Hattersley *et al.* teach away from the use of BMP-4 for chondrogenesis.

The present claims are directed to the use of collagen, not a polysaccharide-collagen cross-linked molecule as disclosed in Heideran *et al.*, and BMP-4, a known protein for induction of osteocytes and bone tissue, not cartilage, as taught in Hattersley *et al.* Therefore, it is not seen how Heideran *et al.* can anticipate the present claims.

The combination of materials in Applicants' claims is not disclosed in Heideran *et al.* Hattersley *et al.* teach away from the use of BMP-4 for use on cartilage or soft tissue. If anything, teachings of the art show that BMP-4 is used to make bone, not cartilage. The Examiner states that chondrogenesis is inherent (Advisory Action, page 2), but the Examiner has cited no scientific support for that statement. One cannot place BMP-4 into the body in the hope that the processes that it induces stop at any transitional phase during the growth or repair process. As stated in Hattersley *et al.*, one needs BMP-12, 13, or 52 to induce chondrocytes or cartilaginous tissue. Hattersley *et al.* teach that BMP-4 will not do it. See

Hattersley *et al.*, column 2, lines 53 through column 3, lines 17. Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner also maintains the rejection under 35 USC 102(e) over Hattersley *et al.* As pointed out in Applicants' previous response, in Hattersley *et al.* there is a requirement that there be present a BMP-12-related sub-family of proteins in order to induce cartilaginous tissue. The osteogenic proteins, such as BMP-4, will not suffice. As previously pointed out by Applicants, Examples 2, 5, 6, and 7 in Hattersley *et al.* prove that the BMP-12 sub-family protein, in this case BMP-13, is necessary for chondrocyte induction and differentiation. An osteogenic protein, such as BMP-2 results in expression of bone phenotypes, not cartilage phenotypes. Therefore, the teaching of Hattersley *et al.* is that no amount of one of the osteogenic proteins, such as BMP-4 or BMP-2, can differentiate chondrocytes, that is, induce cartilage formation. They can only produce bone when used without BMP-12, 13, or 52. Therefore, the language in Applicants' claims of "an effective amount of BMP-4 sufficient to induce or enhance chondrogenesis" is not anticipated by either Heideran *et al.* or Hattersley *et al.*, since there can never be an effective amount of BMP-4 sufficient to induce or enhance chondrogenesis, as taught by Hattersley *et al.* Accordingly, it is submitted that neither reference anticipates the claimed invention and withdrawal of the rejections is respectfully requested.

It is respectfully requested that this amendment be entered and the application be passed to issue.

Respectfully submitted,

BEYER WEAVER & THOMAS, LLP



Reginald J. Suyat

Reg. No. 28,172

P.O. Box 778
Berkeley, CA 94704-0778
(510) 843-6200